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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/890,936	11/07/2001	Olle Korsgren	KORSGREN-1	9165

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EXAMINER
JAGOE, DONNA A

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/890,936	KORSGREN ET AL.	
	Examiner	Art Unit	
	Donna Jagoe	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,8,9,11,14,26 and 27* is/are pending in the application.

4a) Of the above claim(s) *14 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,8,9,11 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments filed December 10, 2007 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 4, 8, 9, 11, 14, 26 and 27 are pending in this application. Claims 14 and 26 are withdrawn. Claims 4, 8, 9, 11 and 27 are rejected.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 4, 8, 11 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Wagner et al. DE 196 23 440 A 1.

Wagner et al. teach method of use of anticoagulants such as heparin, hirudin and Marcumar and derivatives thereof in connection with transplantation of insulin producing cells such as islets of Langerhans (see claim 8). The cells *may* be in the form of microencapsulated islets (see figure 1 and claim 10) and where immunosuppression can be an issue, see "Islet Transplant Info" that teaches that immunosuppression and/or

appropriate drugs, such as Zenapax should be used to address the issue. The abstract for Wagner et al. teach that the immobilized material is insulin, proinsulin and/or organ cells of xenogenic or autogenic origin (islets of Langerhans, etc.) and the system contains an agent to inhibit or suppress blood agglutination, agglomeration antagonists, heparin, hirudin, marcumar and their derivatives. Wagner discloses that the islets *may* be microencapsulated. Additionally, *if* the cells are microencapsulated, they are first mixed with the anticoagulant material. This step of mixing the anticoagulant material anticipates the herein rejected claims. Regarding the term "incubation" in new claim 27, dictionary.com defines incubate as "to maintain at a favorable temperature and in other conditions promoting development". The islet cells are mixed with the anticoagulant material, such as heparin, to suppress blood agglutination. This would encompass maintaining favorable conditions to promote development.

Claims 4, 8, 11 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by Soon-Shiong et al. U.S. 5,705,270 A.

Soon-Shiong et al. teach microcapsules containing biological material such as islet of Langerhans cells coated with polymerizable materials (see abstract, see also claim 3). The microcapsules are covalently linked with heparin (see claim 5). Soon-Shiong et al. teach encapsulation of islets of Langerhans for treatment of diabetes (column 4, lines 1-4) to prevent the detrimental effects of capsule instability on the encapsulated biologically active material e.g. loss of immunoprotection for the encapsulated material is minimized (column 3, lines 61-66). Additionally, note that there is no provision in the instant claims that deals with the immunosuppression issue,

without which, the transplanted islet cells would be rejected (see Islet Transplant Info). The instant specification describes immobilizing heparin according to a method developed by Corline Systems AB disclosed in WO 93/05793 (page 4 of the instant specification). The heparin in WO 93/05793 appears to be immobilized (conjugated) with a polymer comprising a substantially straight-chained organic homo or hetero polymer having a number of functional groups distributed along the polymer backbone chain via which groups at least about 20 molecules (see page 7 of WO 93/05793). While applicant asserts that the heparin is not in microcapsules, it appears that it is similarly coated and as such, must form micro (or macro) capsules if applicant has followed the technique of Corline Systems AB as recited in applicants' specification. Regarding new claim 27 drawn to incubating the isolated islets in a solution of heparin, dictionary.com defines incubate as "to maintain at a favorable temperature and in other conditions promoting development". Although Soon Shiong does not teach "incubation", favorable conditions are maintained to promote polymerization of the heparin and islet cells.

Claims 4, 8, 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Nomura et al. (AG from IDS dated 11/17/03).

Nomura et al. teach islet transplantation for the treatment of type I diabetes after the islets cells were collected and administered with various doses of heparin (page 1849, column 1, paragraph 3).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 9 rejected under 35 U.S.C. 103(a) as being unpatentable over Soon-Shiong et al. U.S. 5,705,270 A and Wagner et al. DE 196 23 440 A 1 as applied to claims 4, 8, 11 and 27 above, and further in view of Couser et al. 1995.

Couser et al. teach that complement is a major mediator of tissue injury in several types of glomerulonephritis (see abstract) and that an inhibitor of complement activation, sCR1 has shown beneficial effects on several forms of tissue injury including xenograft transplantation (page 1892, column 1, 1st full paragraph).

Soon-Shiong et al. teach microcapsules containing biological material such as islet of Langerhans cells coated with polymerizable materials (see abstract, see also claim 3). The microcapsules are covalently linked with heparin (see claim 5). Soon-Shiong et al. teach encapsulation of islets of Langerhans for treatment of diabetes (column 4, lines 1-4) to prevent the detrimental effects of capsule instability on the encapsulated biologically active material e.g. loss of immunoprotection for the encapsulated material is minimized (column 3, lines 61-66). Wagner et al. teach method of use of anticoagulants such as heparin, hirudin and Marcumar and derivatives thereof in connection with transplantation of insulin producing cells such as islets of Langerhans (see claim 8). Davis teaches that the formation of complement is a problem and results in HAR during xenotransplantation.

One of ordinary skill in the art would have administered an inhibitor of complement formation such as sCR1 during islet transplantation since it was well known in the art at the time the invention was made that the formation of complement results in tissue injury and that Couser et al. teach that an inhibitor of complement activation, sCR1 has shown beneficial effects on several forms of tissue injury including xenograft transplantation (page 1892, column 1, 1st full paragraph).

Response to Arguments

Regarding withdrawn claims 14 and 26, as noted in the office action dated March 21, 2006, claim 14 was withdrawn because it was a newly submitted claim directed to an invention that was independent or distinct from the invention **originally claimed**. Please refer to the office action for any further clarification. Claim 26 was added in the claim set submitted June 21, 2006. The claim was withdrawn as directed to an invention that is independent or distinct from the invention originally claimed in the office action mailed January 5, 2007. Please refer to the office action mailed for any further clarification on withdrawn claims.

Regarding applicants remarks drawn to the Declaration of Professor Shapiro and Dr. Larsson, please see "Response to Declaration" below.

Applicant asserts that the interpretation of Wagner “makes no sense, because if cells of Wagner were first mixed with an anticoagulant and then encapsulated as proposed by the examiner at page 4 of the office action, the anticoagulant could not function because the anticoagulant would then be sealed within the microcapsule. In response, Wagner discloses that the islets *may* be microencapsulated. Additionally, *if* the cells are microencapsulated, they are first mixed with the anticoagulant material. The issue here is not whether Wagner's invention is enabled, it is whether it anticipates the instant claims as presented. Applicant asserts that it is "an insoluble polymer shell, around the islets". The examiner cannot find any reference in Wagner drawn to "an insoluble polymer shell around the islets" and would welcome the Applicant to point to page and line to point out this attribute of the invention.

Applicant asserts that Soon-Shiong is "very complicated, relying on photo induced polymerization". Soon-Shiong et al. teach microcapsules containing biological material such as islet of Langerhans cells coated with polymerizable materials (see abstract, see also claim 3). The microcapsules are covalently linked with heparin (see claim 5). The instant specification describes immobilizing heparin according to a method developed by Corline Systems AB disclosed in WO 93/05793 (page 4 of the instant specification). The heparin in WO 93/05793 appears to be immobilized (conjugated) with a polymer comprising a substantially straight-chained organic homo or hetero polymer having a number of functional groups distributed along the polymer backbone chain via which groups at least about 20 molecules (see page 7 of WO 93/05793). While applicant asserts that the heparin is not in microcapsules, it appears that it is similarly coated and as such, must form micro (or macro) capsules if applicant has followed the technique of Corline Systems AB as recited in applicants specification. Claims are not construed in a vacuum, but rather in the context of the intrinsic evidence, viz, the other claims, the specification and the prosecution history. While photo polymerization is not the only method disclosed in Soon-Shiong, if it were the only option for polymerization, the comprising language of the instant claims does not exclude "photo-polymerization".

Applicant states that in the rejection of claim 9, it was not explained how or why Wagner and Soon-Shiong would be combined together with Couser.

The claim is drawn to the method according to claim 4 wherein the clotting inhibiting agent is supplemented by an inhibitor of complement.

Couser et al. provides motivation to employ complement because it teaches that complement is a major mediator of tissue injury in several types of glomerulonephritis (see abstract) and that an inhibitor of complement activation, sCR1 has shown beneficial effects on several forms of tissue injury including xenograft transplantation (page 1892, column 1, 1st full paragraph). One of ordinary skill in the art would have administered an inhibitor of complement formation such as sCR1 during islet transplantation since it was well known in the art at the time the invention was made that the formation of complement results in tissue injury and that Couser et al. teach that an inhibitor of complement activation, sCR1 has shown beneficial effects on several forms of tissue injury including xenograft transplantation (page 1892, column 1, 1st full paragraph).

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant again states that a mailing date is not on the Interview Summary and has still not received a “mailed” copy of the interview summary. Applicant is instructed to view Pair for the document marked "Interview Summary" dated August 9, 2007.

Response to Declaration under 37 CFR 1.132

The Larsson Declaration under 37 CFR 1.132 filed December 10, 2007 is sufficient to overcome the rejection of claims 4, 8, 9 and 11 based upon a lack of written description requirement under 35 U.S.C. §112 first paragraph.

The Larsson Declaration under 37 CFR 1.132 filed December 10, 2007 is insufficient to overcome the rejection of claims 4, 8 and 11 based upon the stated prior art as set forth in the previous office action and above because: Wagner refers to a product characterized by an Immobilization system of a porous and hollow material and Wagner mentions heparin among other possibilities used to antagonize agglomerization and applicant cannot find a disclosure that islet cells are combined with heparin and encapsulated with a polymer such as alginate. In response, Wagner teaches microcapsulation of individual islets with alginates (see page 6). See patent claims drawn to the immobilized organic material (such as islet cells) implanted (claim 1) with agents to prevent or suppress agglomeration of the blood (patent claim 6) such as heparin, hirudin, marcumar or their derivatives and or modifications used to antagonize agglomeration (patent claim 7). Declarant asserts that "Wagner states that most of the microcapsules and the diameter of half a millimeter have a volume several times larger than that of the islets of Langerhans which are 5—300 μm in size". Declarant's argument is irrelevant to the claims instantly presented. The microcapsules of Wagner are not excluded from the instant claims, the claim language *comprising* leaves the claim open for the inclusion of unspecified ingredients, even in major amounts. As stated in the previous office action, and repeated above, the instant specification relies

on Corline Systems AB wherein the heparin is immobilized (conjugated) with a polymer having a substantially straight chained organic homo or hetero polymer. Declarant has not clearly pointed out the novelty of the instant invention as represented by the instant claims. Regarding Soon-Shiong et al., Declarant states that "the preferred heparin material used in the present invention is a water soluble substance that is adsorbed onto the islet surface and there is no cross-linking and no ability of the heparin or Corline Heparin conjugate to cross link". In response, the instant specification teaches polymerization which is an interchangeable term with "cross-link" (dictionary.com defines "cross link" as covalent bonds linking one polymer chain to another). Regarding Declarant's statement that Nomura et al.'s administration of systemic heparin is likely to generate bleeding complications, applicant appears to confuse the requirements for patentability with those of receiving FDA approval. See e.g. In re Anthony, 414 F.2d 1383, 1395, 162 USPQ 594, 604 (CCPA 1969). Consequently, this argument does not raise an issue of material fact. In response to Declarant's arguments against the references individually, such as Couser et al., one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

The Shapiro Declaration under 37 CFR 1.132 filed December 10, 2007 is sufficient to overcome the rejection of claims 4, 8, 9 and 11 based upon a lack of written description requirement under 35 U.S.C. §112 first paragraph.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-0576. The examiner can normally be reached on Monday through Friday from 8:00 A.M. - 4:30 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Donna Jagoe
Examiner
Art Unit 1614

May 19, 2008

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614